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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHANG, CELIA C	
ART UNIT	PAPER NUMBER
1625	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/577,940	LOHRAY, BRAJ	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 22-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/8/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group III, claims 10-21 in the reply filed on Jun. 8, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 10-21 are prosecuted. Claims 1-9, 22-24 are withdrawn from consideration per 37 CFR 1.142(b).

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 10-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Please note that it is unclear what does "form I" mean. No definition of what constitutes form I. Is the material the same as described in US 4,847,265 i.e. having a mp or 184±0.3 or is it the same as those material disclosed in US 6,429,210 or is it the same as those clopidogrel bisulfate disclosed and claimed in copending US20060264636 such as clopidegrel of fig. 1 or 2 etc. Absent of explicit definition of what "form I" constitutes, no standard definition can be found for crystalline forms without its chemical identity i.e. structural formula and **all** its physical properties.

3. Claims 10-18, 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification provided no definition of what is a "suitable solvent" or definition of the product such solvent will be making i.e. what is "form I". Process of making specific crystalline form is highly unpredictable (see KirkOthmer entire article). Absent of clearly description of what is the process making and absent of clearly guidelines of what are the

solvents of any operability, the specification failed to describe the claimed process with any and all "suitable solvent".

4. Claims 10-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case:

Process of making polymorphic forms of a defined compound is very specific and unpredictable. The state of the art of polymorph recovery is highly unpredictable. See for example *Kirk-Othmer Encyclopedia of Chemical Technology* Copyright © 2002 by John Wiley & Sons, Inc., pp. 95-147, Article Online Posting Date: August 16, 2002 (provided in previous office action). This article indicates that many uncertain factors determine morphology, and specifically that the appearance of the crystalline product and its processing characteristics (such as washing and filtration) are affected by crystal habit (i.e., the general shape of a crystal). Relative growth rates of the faces of a crystal determine its shape. Faster growing faces become smaller than slower growing faces and, in the extreme case, may disappear from the crystal

altogether. Growth rates depend on the presence of impurities, rates of cooling, temperature, solvent, mixing, and supersaturation. Furthermore, the importance of each of these factors may vary from one crystal face to another, see page 114.

The reference also teaches that polymorphism is a condition wherein crystalline form is intimately associated with processing ("*Polymorphism* is a condition in which chemically identical substances may crystallize into different forms. Each form is, however, only stable (thermodynamically) in a certain range of temperature and pressure. In the case of ambient pressure, eg, ammonium nitrate exhibits four changes in form between -18 and 125°C:

Transitions from one polymorphic form to another may be accompanied by changes in process conditions (temperature, pressure, shear or solution composition), transitions from one polymorphic form to another and lead to formation of a solid product with unacceptable properties (eg, melting point or dissolution rate).

The Mukarram et al. WO 2005/012300 reference provided evidence that the instant claimed process is inoperable in producing form I exclusively (see '300 p.3 paragraphs after structural formula). Specifically, Mukarram '300 disclosed that form I without contamination of other forms would have a higher melting point between 198-200°C. In the instant application, no definition of what constitute "form I" with identifiable physical characteristics. It is unclear what was the nature of the product i.e. same as US 4,847,265 or not. The specification exclusively exemplified using a single crystalline solvent of n-hexanol with concentrated/dilute sulfuric acid. No description or measurement in comparison with the prior art products as to provide sufficient information of what was made.

In the prior art, it was also evidenced that when crystallization was conducted under the conditions and parameters of Lifshitz et al. US 6,767,913, using 2-propanol, the clopidogrel hydrogen sulfate form IV was formed (see col. 21, lines 58-60) after reflux and cooled to room temperature. When crystallization was conducted under the conditions and parameters of Lifshitz et al. '913, using 2-butanol, the clopidogrel hydrogen sulfate form V is formed (see col. 22, lines 35-40) after reflux and cooled to room temperature.

In view of the high degree of unpredictability and the evidence in the prior art that solvents, temperature, time, mechnical sterring etc. are all critical elements in controlling purity of "forms", the "claimed scope" lacks descriptive and enablement supported from the specification.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
> The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 10-19, 20 are rejected under 35 U.S.C. 102(b) or (e) as being clearly anticipated by Bardore et al. US 4,847,265 (1449) ; Bousquet et al. US 6,429,210 (1449); Valeriano et al. US 6,800,769; Lifshitz-Liron et al. US 7,074,928 (1449) or Mukarram et al. US 7,291,735.

See Bardore et al. '265, col. 6, example 1(e) lines 47-64;

Bousquet et al. '210, col. 9, lines 44-60, example 1B;

Valeriano et al. '769, col. 13 example 9;

Lifshitz-Liron et al. '928, col. 19-20 examples of form I;

Mukarram et al. '735, col. 4, example (b).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 10-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bardore et al. US 4,847,265 or Bousquet et al. US 6,429,210; Valeriano et al. US 6,800,769; Lifshitz-Liron et al. US 7,074,928 or Mukarram et al. 7,291,735 in view of Lifshitz-Liron et al. US 7,074,928 or Mukarram et al. '735.

Determination of the scope and content of the prior art (MPEP §2141.01)

Bardore et al. '265 or Bousquet et al. '210 or Mukarram et al. '735 disclosed process of making the same claimed product clopidogrel bisulfate form I, see '265 col. 6, example 1(e) lines 47-64; '210 col. 9, lines 44-60, example 1B; Valeriano et al. '769, col. 13 example 9; or Mukarram et al. '735, col. 4, example (b). The anticipatory nature of the references have been clearly identified in the previous section and hereby incorporated by reference.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims with broad scope of starting material (such as the limitation of dependent claims 18 and 19) and the prior art in using a bisulfite precursor salt has been taght by Valeriano et al. '769 that using an enantiomerically pure species such as the Camphor salt is an optional choice. Further difference between the instant claims with broad scope encompassed by "suitable solvents" and the listed specific solvents in claim 20 and the prior art process is that instead of acetone or ethylacetate, the instant claims employed a different solvent. Lifshitz-Liron et al. US 7,074,928 taught that variation of solvent such as ether may be employed to obtain the same product (col. 19-20 examples of form I). Mukarram et al. '300 taught that the same product obtained with acetone can be obtained using solvents such as alcohol or ether (see col. 2, paragraph after structural formula).

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art would be motivated to employ variation of solvents in obtaining the same product because one has been suggested that similar organic solvent would give the same product as evidenced by the per ponderous of references i.e. '265, '210, '928 and '300, that changing solvents is a routine choice by the person having ordinary skill and hexanol is a common laboratory solvent for one having ordinary skill to choose. Enhancing purity is always a desirable motivation for medicinal chemists, therefore, one would be motivated by the suggestion that purity would be changed by routine variation of laboratory solvents (see i.e. Mukarram et al.) and picking and choosing alternative laboratory available solvents to modify the prior art process. In absence of unexpected result, changing an *effect* oriented parameter in chemical process is prima facie obvious in the chemical art.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Sept. 22, 2009

/Celia Chang/
Primary Examiner
Art Unit 1625